Summary for Clinicians: Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

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Evidence-based guidelines for the management of idiopathic pulmonary fibrosis (IPF) were updated in 2022 in a multidisciplinary discussion (MDD) by a panel of experts appointed by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society (1). Topics from earlier guidelines that were addressed included radiological and histopathological features of usual interstitial pneumonia (UIP), transbronchial lung cryobiopsy (TBLC), and genomic classifier (GC) testing for the diagnosis of IPF and the use of antacid medications and antireflux surgery for treatment of IPF. Additionally, the term progressive pulmonary fibrosis (PPF) was defined to describe interstitial lung diseases (ILDs) other than IPF that progress to fibrosis, and treatment of PPF with antifibrotic medications was explored. Guidelines have different implications for patients, clinicians, and policymakers (Table 1). This summary is intended to provide the practicing clinician with key points from the guideline.

IPF: Update on Diagnosis and Treatment

IPF is a specific type of chronic progressive fibrosing ILD of unknown cause. A diagnosis requires: *1*) the exclusion of other known causes of ILD and *2*) the presence of a UIP pattern on high-resolution chest computed tomography (HRCT) or a specific combination of HRCT and histopathological patterns in patients subjected to tissue sampling (Figure 1).

Radiographic Features of UIP

Honeycombing and traction bronchiectasis/bronchiolectasis are closely related and likely represent a remodeling continuum of fibrosis. Although the UIP pattern is a hallmark for IPF, the panel emphasized that it can also be seen in fibrotic hypersensitivity pneumonitis, connective tissue disease, or exposure-related ILDs. Although patients with the UIP and probable UIP patterns exhibit similar disease behavior and likelihood of UIP on histopathology, the committee retained the four radiographic categories with minor modifications for several reasons (Table 2). Correlations between a probable HRCT UIP pattern and UIP histopathology, reported to be 80–85%, are from expert centers, so predictive performance in other settings is unknown. Patients with a probable UIP pattern may have better survival than patients with a UIP pattern. Finally, the predictive value for radiographic probable UIP pattern is lower for mild fibrosis and in younger patients, so this pattern may overlap other fibrotic ILDs more than an HRCT UIP pattern. Despite preserving the distinction between the UIP and probable UIP HRCT patterns, the committee affirmed that the diagnostic approaches to these categories are similar and a diagnosis of IPF can be made without histopathological confirmation with a UIP or probable UIP pattern in the appropriate clinical context (Figures 1 and 2).

Histopathological Features of UIP

The committee reviewed and confirmed the histopathological criteria that define UIP and probable UIP patterns. UIP consists of:

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Table 1. Implications of clinical guideline recommendations by stakeholder

Stakeholder	Strong Recommendation	Conditional Recommendation
Patients	The majority of patients would want the recommended course of action in this situation, and only a small number would not.	Many patients in this situation would prefer the recommendation, but a substantial number may not. This is an opportunity for shared decision-making between the clinician and patient.
Clinicians	Most individuals should receive the course of action that is recommended. There is a low chance that additional formal decision aids are needed to help individuals make decisions consistent with their values and preferences, and adherence to this recommendation could be used as a performance indicator or quality criterion.	Different choices will be applicable to different patients, and additional factors will need to be considered in addition to the recommendation for a patient to make a decision according to their values and preferences. Decision aids may be needed to assist individuals in making their best choice. This is an opportunity for shared decision-making between the clinician and patient.
Policymakers	The recommendation can be widely adapted as policy and can be used for performance indicators.	Policy making will require substantial additional debate and involvement of many and/or additional stakeholders. The likelihood of regional variance is also higher, and performance indicators would need to take into consideration any additional deliberation that has occurred.

Best practice statements: no appropriate alternative course of action for all stakeholders other than the recommendation.

1) patchy dense fibrosis with architectural distortion, *2*) predilection of subpleural and paraseptal lung parenchyma, *3*) fibroblast foci, and *4*) absence of features suggesting an alternative diagnosis. A probable UIP pattern includes some of these features in the absence of features suggesting an alternative diagnosis (2). The committee noted that TBLC, compared with surgical lung biopsy (SLB), is more likely to exhibit a probable UIP pattern given the limited sampling of the subpleural lung (3). However, in the context of an MDD, combining UIP and probable UIP histopathological patterns from TBLC results in similar rates of diagnostic agreement with SLB.

TBLC

- *For patients with newly detected ILD of undetermined type who are clinically suspected of having IPF, the panel suggested that TBLC be regarded as an acceptable alternative to SLB for making a histopathological diagnosis in medical centers with experience performing and interpreting TBLC (conditional recommendation, very low-quality evidence).*

The overall diagnostic yield of TBLC, defined as the number of procedures yielding a histopathological diagnosis divided by the total number of procedures performed, was

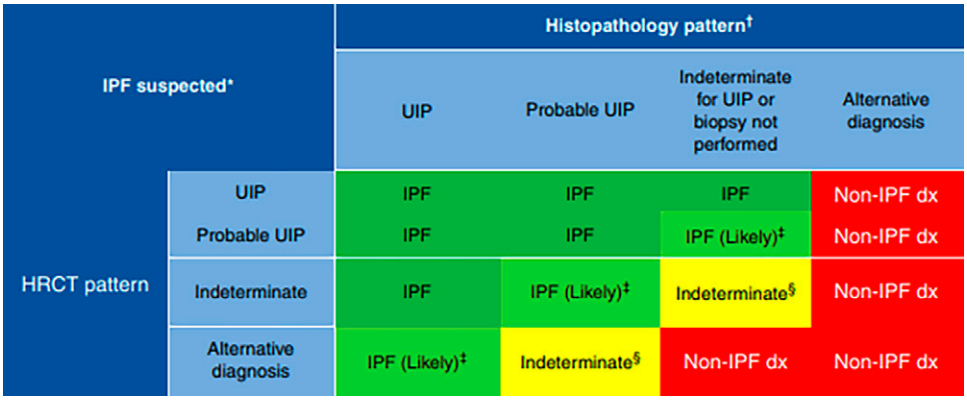

Figure 1. Idiopathic pulmonary fibrosis (IPF) diagnosis on the basis of high-resolution computed tomography (HRCT) and biopsy patterns developed using consensus by discussion. *"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age greater than 60 years. Middle-aged adults (>40 and <60 years old) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis. †Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy. ‡IPF is the likely diagnosis when any of the following features are present: *1*) moderate to severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man older than 50 years or in a woman older than 60 years, *2*) extensive (>30%) reticulation on HRCT and age more than 70 years, *3*) increased neutrophils and/or absence of lymphocytosis in bronchoalveolar lavage fluid, and *4*) multidisciplinary discussion produces a confident diagnosis of IPF. §Indeterminate for IPF: *1*) without an adequate biopsy remains indeterminate and *2*) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation. Adapted from Reference 1. dx = diagnosis; UIP = usual interstitial pneumonia.

Table 2. High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis

	HRCT Pattern			
	UIP Pattern	**Probable UIP Pattern**	**Indeterminate for UIP**	**CT Findings Suggestive of an Alternative Diagnosis**
Level of confidence for UIP histology	Confident (>90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (⩽50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • Occasionally diffuse • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribronchovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking-related IP)
CT features	• Honeycombing with or without traction bronchiectasis/ bronchiolectasis • Presence of irregular thickening of interlobular septa • Usually superimposed with a reticular pattern, mild GGO • May have pulmonary ossification	• Reticular pattern with traction bronchiectasis/ bronchiolectasis • May have mild GGO • Absence of subpleural sparing	• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings ◦ Cysts (consider LAM, PLCH, LIP, and DIP) ◦ Mosaic attenuation or three-density sign (consider HP) ◦ Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis) ◦ Profuse centrilobular micronodules (consider HP or smoking-related disease) ◦ Nodules (consider sarcoidosis) ◦ Consolidation (consider organizing pneumonia, etc.) • Mediastinal findings ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD)

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IP = interstitial pneumonia; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; UIP = usual interstitial pneumonia.
The previous term, "early UIP pattern," has been eliminated to avoid confusion with "interstitial lung abnormalities" described in the text. The term "indeterminate for UIP" has been retained for situations in which the HRCT features do not meet UIP or probable UIP criteria and do not explicitly suggest an alternative diagnosis. Adapted from Reference 1.

79%. Two studies reported agreement between diagnostic interpretation of TBLC and SLB samples. The larger study demonstrated 70.8% agreement, which increased to 76.9% after MDD. *Post hoc* analysis suggested that agreement between TBLC and SLB improved with more TBLC samples. The smaller study, however, reported diagnostic agreement of only 38%. The notable complications of TBLC included pneumothorax in 9% and any bleeding in 30%. Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare (2). Evidence suggests that patients who have nondiagnostic TBLC are also likely to have nondiagnostic findings on SLB. The committee compared the diagnostic yield of TBLC (79%) favorably to the yield of SLB (90%) and considered that TBLC is less invasive and less costly. As a result, the panel conditionally recommended TBLC if performed in experienced centers with standardized protocols.

GC Testing

- *For patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy, the panel made no recommendation for or against the addition of GC testing for the purpose of diagnosing UIP (low-quality evidence).*

The GC identifies RNA sequences of lung tissue obtained via transbronchial forceps biopsies to predict the presence of a UIP histopathological pattern. A meta-analysis of four available studies demonstrated a pooled sensitivity of 68% and specificity of 92% for a UIP pattern when comparing versus samples obtained by SLB, TLBC, or MDD as the reference standard (4). Although the committee recognized that the high specificity may reduce the need for more invasive histopathological sampling by SLB or TBLC, there was insufficient agreement among committee members to make a recommendation for several reasons. The low sensitivity will result in many false negatives, the result of which needs to be better understood. The GC does not provide the granular details that histopathology provides, and its use is only studied in the context of an MDD. The importance of identifying a UIP pattern is less clear in the context of expanding antifibrotic indications. Finally, the GC is not yet widely available.

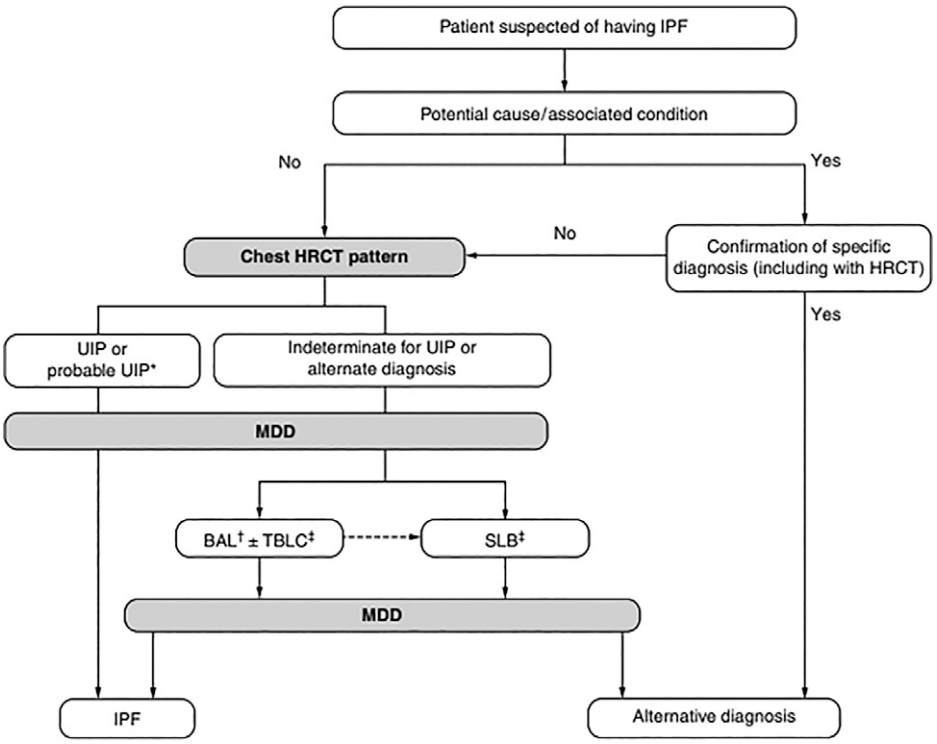

Figure 2. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF) developed using consensus by discussion. *Patients with a radiological pattern of probable usual interstitial pneumonia (UIP) can receive a diagnosis of IPF after multidisciplinary discussion (MDD) without confirmation by lung biopsy in the appropriate clinical setting (e.g., 60 years old, male, smoker). Bronchoalveolar lavage (BAL) may be appropriate in some patients with a probable UIP pattern. †BAL may be performed before MDD in some patients evaluated in experienced centers. ‡Transbronchial lung cryobiopsy (TBLC) may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations as described in the text. A subsequent SLB may be justified in some patients with nondiagnostic findings on TBLC. HRCT = high-resolution computed tomography. Adapted from Reference 1.

Evidence-based Recommendations for Treatment of IPF

Antacid Therapy

- *For patients with IPF and confirmed gastroesophageal reflux (GER), with or without symptoms of gastroesophageal reflux disease (GERD), the panel suggests not treating patients with antacid medication for the purpose of improving respiratory outcomes (conditional recommendation, very low-quality evidence).*

No studies were identified that stratified patients as having or not having confirmed GERD, so all studies in the review included patients with IPF regardless of confirmation of GER. Fifteen studies were identified, with 10 evaluating proton pump inhibitors or histamine-receptor 2 antagonists and 5 evaluating only proton pump inhibitors. Antacid therapy had no statistically significant effect on disease progression, lung function, mortality, exacerbations, or hospitalizations (5). The committee noted, however, that the evidence was of very low quality and indirect in that many studies were observational and the studies included patients in whom GER was not confirmed. The committee noted that antacid therapy may still be appropriate for patients to improve GER-related symptoms and outcomes.

Antireflux Surgery

- *For patients with IPF and confirmed GER, with or without symptoms of GERD, the panel suggested not referring patients with IPF for antireflux surgery for the purpose of improving respiratory outcomes (conditional recommendation, very low-quality evidence).*

Four studies were identified by the review, with only one being a randomized controlled trial. No statistically significant differences were identified in mortality, exacerbations, hospitalizations, or lung function. The data on disease progression, a composite outcome of various components, was mixed, with some component outcomes (>10% decrease in forced vital capacity [FVC] or death, >10% decrease in FVC, acute exacerbation, or death) being statistically significant depending on the method of analysis. The 30-day complication and severe complication rates from surgery were 15% and 9%, respectively (5). As a result of the absence of definite statistically significant benefits and the presence of the noted complication rates, the committee suggested against antireflux surgery for improvement of respiratory outcomes in patients with IPF.

Diagnosis and Treatment of PPF in Fibrotic ILD Other than IPF

Definition of PPF

In patients with ILD of known or unknown etiology other than IPF with radiological

Table 3. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

Definition of abbreviations: D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.
*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography. Adapted from Reference 1.

evidence of pulmonary fibrosis, the panel defined PPF as meeting at least two of the following three criteria within a 1-year period with no other explanation: *1*) worsening respiratory symptoms, *2*) physiological evidence of disease progression, and/or *3*) radiological evidence of disease progression. The panel emphasized that PPF is defined separately from IPF, that PPF is not a diagnosis and so is agnostic to the underlying condition, and that it is associated more with prognosis. PPF was used in place of progressive fibrosing ILD because disease progression occurs as a result of PPF beyond the interstitial space, and PPF is more congruent with pulmonary fibrosis, a term used by clinicians and patients broadly that is easier to translate globally. Physiological criteria and radiological criteria to define PPF are in Table 3.

Evidence-based Recommendations for Treatment of PPF Other than IPF

Pirfenidone

- *For patients with non-IPF ILD manifesting PPF in general and in specific types of non-IPF ILDs manifesting PPF, the panel recommends further research into the efficacy, effectiveness, and safety of pirfenidone (very low-quality evidence).*

Antifibrotic medications such as pirfenidone have been shown to decrease disease progression in IPF. The panel conducted a systematic review and meta-analysis to assess the impact of pirfenidone on lung function, disease progression, respiratory symptoms, adverse events, and mortality in PPF. Meta-analysis of available studies revealed that pirfenidone reduced the decrease in FVC by 100 ml and FVC% predicted by 2.3% over 24 weeks compared with placebo (6). There was no statistically significant difference in other lung function parameters, respiratory symptoms, or mortality. The pirfenidone group did have increased risk of adverse events, including gastrointestinal discomfort and photosensitivity. However, the quality of evidence was very low because of the limited number of studies with small sample sizes and early termination in one. No recommendation was made because a third of the panel abstained from voting as a result of insufficient evidence. The panel as a whole acknowledged that pirfenidone is a promising therapy for non-IPF PPF, but additional studies with larger sample sizes and clear delineation of each type of ILD are needed.

Nintedanib

- *For patients with non-IPF ILD manifesting PPF who have failed standard management for fibrotic ILD, the panel suggests nintedanib for the treatment of PPF (conditional recommendation, low-quality evidence). Additionally, the panel recommends research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF (low-quality evidence).*

Nintedanib is an antifibrotic medication that has been shown to decrease disease progression in IPF. The panel conducted a systematic review and meta-analysis to assess the impact of nintedanib on disease progression, respiratory symptoms, adverse events, and mortality in PPF. Meta-analysis of available studies revealed that nintedanib reduced the mean annual decrease in FVC by 107 ml compared with placebo. This reduction was 128 ml among patients with a radiological UIP pattern, 75.3 ml among patients with a radiological non-UIP pattern, 106.2 ml if the underlying ILD was connective tissue disease–related, 141.7 ml for fibrotic nonspecific interstitial pneumonias, and 252.8 ml for fibrotic occupational lung disease–related ILD (7). There was no statistically significant difference in respiratory symptoms or mortality. The nintedanib arm did have increased gastrointestinal adverse events, however. The quality of evidence was deemed to be low because of the small number of studies and small sample sizes, but a conditional recommendation was made for PPF in general because there was a statistically significant reduction in disease progression, with the key adverse events being reversible with discontinuation of therapy. There were insufficient data to address each ILD by type, and therefore a research recommendation is made to assess the effect of nintedanib in different types of ILD.

Conclusions

This guideline updates previously published guidelines on the diagnosis and treatment of IPF and also defines the entity of and makes treatment recommendations for PPF. The recommendations are not mandates; aim to provide guidance to clinicians in areas of new, uncertain, or weak evidence; and should be revisited as new evidence is available. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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